

Imaging techniques in ALS

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Abstract

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease characterized by degeneration of both upper and lower motor neuron located in the spinal cord and brainstem. Diagnosis of ALS is predominantly clinical, nevertheless, electromyography and Magnetic Resonance Imaging (MRI) may provide support. Several advanced MRI techniques have been proven useful for ALS diagnosis and, indeed, the combination of different MRI techniques demonstrated an improvement in sensitivity and specificity as far as 90%. This review focus on the imaging techniques currently used in the diagnosis and management of ALS with brief considerations on future applications.

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Introduction

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease that was firstly described by Jean-Martin Charcot (Kumar et al. 2011). It is characterized by degeneration of both upper (UMN) and lower (LMN) motor neuron located in the spinal cord and brainstem (Gordon 1995). Currently, diagnosis of ALS is predominantly based on clinical presentation, progression of symptoms, and exclusion of other diseases. However, electromyography and Magnetic Resonance Imaging (MRI) may support the clinical diagnosis (Andersen et

al. 2012). Although this diagnostic pathway, when made by an experienced clinician, has been proved to be accurate in nearly 95% of patients, it is mandatory to develop early biomarkers in order to facilitate the diagnosis, characterize phenotype and monitor the disease progression (Bowser, Turner, and Shefner 2011; Rowland, Mitsumoto, and Przedborski 2010; Turner et al. 2009).

MRI has been used to detect cerebral signal intensity changes, such as hyperintensity on T2-weighted images (Comi, Rovaris, and Leocani 1999). Although it is true that hyperintense signal along corticospinal tract (CST) extending from the corona radiata to the brainstem is considered the best diagnostic clue for ALS, this finding can be seen in healthy control as well as in other diseases (Caiazzo et al. 2014; Gordon 1995; Ngai et al. 2007). Moreover, several advanced techniques have been proved useful, indeed the combination of different MRI techniques demonstrated an improvement in sensitivity and specificity as far as 90% (Filippini et al. 2010). In spite of these advantages, current guidelines about the management of ALS advocated the use of MRI simply as a tool to exclude mimic lesions (mostly spinal) (Brooks et al. 2000; Filippi et al. 2010; Ludolph et al. 2015).

This review will focus on the imaging techniques currently used in the diagnosis and management of ALS with brief considerations on future applications.

Conventional MRI

The guidelines provided by the World Federation of Neurology Research Group on MNDs and the European Federation of Neurological Societies guidelines on neuroimaging of motor neuron diseases (MNDs) suggest the use of conventional MRI to exclude so-called “mimic” syndromes which may cause UMN and/or LMN signs (Brooks et al. 2000; Filippi et al. 2010; Ludolph et al. 2015).

The best diagnostic clue and most frequent signal changes found in patients with MND is the bilateral hyperintensities along the corticospinal tract (CST) extending from the corona radiata to the brainstem (figure 1), visualized on T2-weighted images, proton density-weighted images (PD), and fluid-attenuated inversion recovery images (FLAIR) (Abe et al. 1997; Bede et al. 2014; Hecht et al. 2001, 2002). This finding can be better appreciated on coronal images following the pyramidal tract downward to the ventral portion of the brainstem and upward to the corona radiata. Although there is a wide consensus on the presence of this signal change, some researchers suggest that it is better demonstrated on FLAIR whilst others deem more reliable T2-WI and PD-WI (Hecht et al. 2001; Hofmann et al. 1998; Peretti-Viton et al. 1999). However, hyperintense signal in CST is not specific for ALS, non quantifiable and often not correlated to clinical signs or disease severity (Winhammar et al. 2005). Healthy individuals and patients that underwent liver transplant showed the same finding;

therefore CST hyperintensities are neither sensitive nor specific (Ngai et al. 2007; Turner 2005).

Cortical atrophy of the frontal lobe, predominantly in the precentral gyrus, has been reported as a common finding in patients with longer disease duration (Comi et al. 1999). Nevertheless atrophy is not consistently detectable on standard MRI and advanced technique can improve its detection (Bowser et al. 2011). Lastly, using conventional imaging it is possible to detect a low signal intensity (hypointense rim) on T2-WI or Gradient-Echo sequences of the pre-central cortex and, specifically, in the primary motor cortex (Hecht et al. 2001; Hofmann et al. 1998). This ribbon-like hypointensity (figure 2) have been recently confirmed using susceptibility-weighted imaging (SWI), quantitative susceptibility mapping (QSM) and 7T scanner (Adachi et al. 2014; Kwan et al. 2012; Prell et al. 2015; Schweitzer et al. 2013). However, it is not specific, can be due to iron and heavy metals accumulation in cortex of aged patients and it is rarely found in daily routine (Ngai et al. 2007; Oba et al. 1993).

Diffusion Weighted Imaging (DWI) and Diffusion Tensor Imaging (DTI)

Diffusion based techniques have a crescent role in diagnosis and management of ALS. DWI may demonstrate a hyperintensity in the CST that can be seen prior to the signal changes in T2WI, moreover the degeneration of white-matter fibres results in significant changes in DTI

(Bowser et al. 2011; Filippi et al. 2010; Kassubek, Ludolph, and Muller 2012; Pradat and El Mendili 2014; Turner et al. 2011). Indeed, in white matter, the diffusion of water molecules occurs preferentially along the axis of orientation of the fibre bundles while and in damaged tracts, molecules water are more freely diffusible generating signal changes in DWI and DTI. Fractional anisotropy (FA) is a value that describes the degree of anisotropy of diffusion and it has values comprised between zero and one with the former expressing an isotropic diffusion and the latter a restriction in all directions. In 1999 Ellis et al. demonstrated a significant decrease in FA in the corticospinal tract (figure 3) (Ellis et al. 1999). Since then, several authors confirmed this finding (Li et al. 2012; Sach et al. 2004; Turner et al. 2009; Valsasina et al. 2007). Moreover, recently, Filippini et al. demonstrated a decrease in FA also in the corpus callosum (CC) suggesting the use of this finding as a biomarker for ALS (Filippini et al. 2010). Indeed degeneration of corpus callosum has been associated with different pattern of motor neuron diseases (MNDs) and disease progression (Müller et al. 2009; Riad, Hathout, and Huang 2011; Unrath et al. 2010; Unrath, Ludolph, and Kassubek 2011; Valsasina et al. 2007).

Structural analysis

Focal brain atrophy is a key feature of ALS, thus structural MRI has been used to detect and quantify that atrophy. High-resolution T1-WI is

acquired using a 1-mm resolution in each direction (figure 4) and can be analysed using two different approaches: voxel-based morphometry (VBM) and surface-based morphometry (SBM). The former analyses grey and white matter volumes in specific brain region whilst the latter measures cortical thickness (Ashburner and Friston 2000; Das et al. 2009; Fischl and Dale 2000).

Although results were inconsistent, several studies showed volume changes in CST, primary motor cortex and frontotemporal cortices using VBM analysis (Agosta et al. 2007; Chang et al. 2005; Chiò et al. 2014; Kassubek et al. 2005; Turner et al. 2007). Interestingly, atrophy in the right precentral gyrus has been consistently associated with ALS and has been proposed as a landmark of disease (Chen and Ma 2010). Following the introduction of SBM analysis, that is more reliable, the reduction in cortical thickness in the motor cortex has been consistently proved and it has also been correlated with disease progression (Agosta et al. 2009, 2012; Roccatagliata et al. 2009; Verstraete et al. 2012). Structural evaluation of CC have revealed no differences between ALS patients and controls, thus suggesting that there is not a morphological involvement of CC (Chapman et al. 2012; Foerster, Welsh, and Feldman 2013).

Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) is a technique that measures the neurochemical profile within a region of interest. MRS of the

brain evaluates the presence and quantity of a metabolite called N-acetylaspartate (NAA), which is a marker of neuron integrity, and its ratio to choline (NAA:Cho) or creatine (NAA:Cr) as markers of neuronal integrity. In 1994 a study published by Pioro and colleagues demonstrated that there is a significant decrease in NAA:Cr in patients with MND in the primary motor cortex (Pioro et al. 1994). Since then, many studies confirmed the decrease in values of NAA, NAA:Cho and NAA:Cr in the motor cortex and in the CST suggesting a reduced neuronal integrity in that areas (Pohl et al. 2001; Sarchielli et al. 2001; Suhy et al. 2002). Similar changes have been pointed out in the pons and the medulla of patients with ALS (Anon n.d.; Cwik et al. 1998).

Albeit several authors have consistently reported these findings, their role in the diagnosis of ALS is limited because there is a significant overlap with healthy controls (Gredal et al. 1997; Pioro et al. 1994; Pradat and El Mendili 2014). The use of higher magnetic strengths, such as 3-T, can improve the diagnosis of ALS. At higher field there is a greater metabolite spatial resolution that permits a better separation of metabolite signals and might improve their quantification. One of this metabolite that can be identified in the cortex using 3-T magnets is GABA (Bowser et al. 2011; Zhu et al. 2011). GABA can be used as a surrogate marker of excitotoxicity, which has been proved to play a role in pathogenesis of ALS (Foerster et al. 2012; Foerster, Pomper, et al. 2013). Indeed several studies demonstrated a decrease in levels of GABA in the

motor cortex of ALS patients compared with controls (Foerster et al. 2012; Zhu et al. 2011).

In order to corroborate these promising results, multicentre studies should be conducted thus to confirm the potential role of MRS in diagnosis and treatment monitoring of ALS. Nevertheless, MRS is a highly operator-dependent technique, especially at higher fields, with, basically, no standardisation in both acquisition and postprocessing; therefore multicentre studies have significant barriers (Bowser et al. 2011).

Functional MRI

Functional MRI is a rapidly accessible, non-invasive, and radiation-free technique that allows the assessment of brain functioning through the differential magnetic properties of oxygenated and deoxygenated haemoglobin. The technique most often used is called Blood Oxygenation Level-Dependent (BOLD) and, since its introduction in early nineties, its applications in clinical and research settings are constantly increased.

Brain activation studies in ALS patients demonstrated a significant decrease in regional patterns of activation during a motor task paired with activation in other unrelated regions when compared to control groups (figure 5) (Konrad et al. 2002; Tessitore et al. 2006). This finding supports the contrasting hypothesis of cortical reorganization or functional adaptation due to peripheral weakness (Konrad et al. 2002; Schoenfeld et al. 2005). Moreover, an increase in regional activation was reported during

motor imagery with a further increase during follow-up matching the physical impairment (Lulé et al. 2007). A subsequent study using a simple hand motor task corroborated the prognostic implications of brain functional rearrangement in ALS (Poujois et al. 2013).

Resting-state fMRI (rs-fMRI) has the potential to limit the bias due to physical impairment being independent from motor task (Agosta et al. 2011; Greicius et al. 2004). Several studies conducted using rs-fMRI demonstrated wide reorganisation of cerebral networks that correlate with the changes detected with BOLD technique (Agosta et al. 2011, 2013; Douaud et al. 2011; Jelsone-Swain et al. 2010; Verstraete et al. 2010). Other researchers demonstrated a significant decrease of functional connectivity within the sensorimotor network and in brain networks related to cognition and behaviour supporting the idea of a diffuse disease more than a strictly localized alteration (Douaud et al. 2011; Fekete et al. 2013; Jelsone-Swain et al. 2010; Luo et al. 2012; Mohammadi et al. 2009; Tedeschi et al. 2012; Zhou et al. 2013).

According to the EFNS guidelines, fMRI is recommended in the assessment of cognitive network abnormalities in patients with MND (Filippi et al. 2010). However, recent studies have underlined the potential usefulness of task-free fMRI to detect functional changes on a broader scale, which can further exploit the 'network or system failure' model of ALS pathogenesis (Kassubek et al. 2012; Turner et al. 2011).

Spinal Cord Imaging

Spinal cord imaging can constitute a major breakthrough in ASL imaging because it investigates both the upper and lower motor neuron. Despite limits such as the small size of the cord, motion and chemical-shift artefacts, and geometric distortion DTI and MRS have both demonstrated changes in spinal cord that are consistent with those experienced in the brain (figure 6).

DTI confirmed the reduction of FA and the increase of radial diffusivity, especially in the cervical spinal cord (El Mendili et al. 2014; Valsasina et al. 2007). Moreover, Cohen et al. demonstrated that focal atrophy correlates with functional impairment and the combination of focal FA reductions and increase in radial diffusivity are also present in the dorsal cord columns, confirming the involvement of the sensory pathways (Cohen-Adad et al. 2013). Lastly, analysis of spinal cord DTI parameters could allow a further insight of ALS' physiopathology; indeed it can confirm the involvement of sensory pathway and clarify which one of the dying-back and the dying-forward theories is the correct one (Cohen-Adad et al. 2013).

Similarly to DTI, MRS studies were performed at cervical cord level to overcome the limitations stated above. Several studies demonstrated a significant decrease in NAA:Cr and NAA:myo-inositol in patients with ALS (John D Carew et al. 2011; Ikeda et al. 2013). Interestingly these findings

have been reported also in presymptomatic patients with SOD1 mutations (J D Carew et al. 2011).

Frontotemporal Dementia and Amyotrophic Lateral Sclerosis

Frontotemporal Dementia (FTD) is a neurodegenerative disorder which affects primarily in the frontal lobes and in the anterior portions of the temporal lobes (Hodges et al. 2004). ALS and FTD are both multisystem neurodegenerative diseases and, according to their frequent association, they have been advocated as the two poles of a disease spectrum (Clark and Forman 2006; Neumann et al. 2006). Indeed, they share clinical, genetic and pathogenetic characteristics confirming their nature as a continuum disease with different symptoms prevalence (Ling, Polymenidou, and Cleveland 2013; Murphy et al. 2007). Moreover, patients with ALS could demonstrate cognitive impairment whilst patients with FTD could experience MND symptoms (Lomen-Hoerth, Anderson, and Miller 2002; Ringholz et al. 2005).

Several studies have demonstrated common changes in ALS and FTD in the frontal and temporal lobes (Cirillo et al. 2012; d'Ambrosio et al. 2014; Lillo et al. 2012). More recently, common changes have been demonstrated using rs-MRI in the sensorimotor domain and, less frankly, in the connectivity pattern (Trojsi et al. 2014). The latter finding confirmed the theory that these two diseases should be considered as different expression of the same neurodegenerative process.

Summary

MRI constitutes a useful non-invasive tool in the assessment of ALS. Currently, its greatest role is to exclude the presence of a mimic disorder rather than diagnose a patient with ALS. Moreover, MRI has given a deeper insight into the pathophysiology of MND and has clarified the multisystem nature of this disease. The development of advanced techniques in the past few years lead to further application of MRI in the management of ALS. Indeed MRI has been proposed as a biomarker for diagnosis, progression and prognosis.

In conclusion, MRI has a greater potential to aid in terms of increase the characterization of patients with ALS improving in the meantime our understanding of this disease, monitoring its progression and predicting its prognosis. However, further prospective studies are needed with larger cohorts and a multicentre approach.

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Captions:

Figure 1: MRI of patients with clinically diagnosed amyotrophic lateral sclerosis (ALS). In both patients axial T2WI (A and C) and coronal FLAIR (B and D) demonstrate T2 hyperintensity along the corticospinal tract. A and B: 71 years old man; C and D: 65 years old female.

Figure 2: Gradient-Echo sequence (A and B) and Susceptibility-Weighted sequence (C and D) obtained in a patient with clinically diagnosed amyotrophic lateral sclerosis (ALS).

Figure 3: DTI obtained in a patient with clinically diagnosed amyotrophic lateral sclerosis (ALS). Color-coded fractional anisotropy (A and B) and tractography color-coded maps (C). Images demonstrated a slight decrease in FA in the right corticospinal tract consistent with patient's symptoms.

Figure 4: 3D-SPGR T1WI obtained in a patient with clinically diagnosed amyotrophic lateral sclerosis (ALS). Axial projection (A), coronal projection (B) and sagittal projection (C).

Figure 5: fMRI obtained in a patient with clinically diagnosed amyotrophic lateral sclerosis (ALS). Images were acquired during the execution of a “finger tapping” task. There is a significant cortical activity in the ipsi- and contralateral sensorimotor cortex, supplementary motor area and in the basal ganglia.

Figure 6: Spinal MRI of a male patient with clinically diagnosed amyotrophic lateral sclerosis (ALS). Axial T2WI (A) and Sagittal STIR (B) do not demonstrate signal changes related to ALS.